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TITLE: **F^{18} EF5 PET/CT Imaging in Patients with Brain Metastases from Breast Cancer**

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14. ABSTRACT

The aim of this study is to estimate the degree of residual hypoxia after whole brain radiation therapy in patients with brain metastases from breast cancer as quantified by F18 EF5 PET/CT imaging. There has been great difficulty in accruing patient to this study due to the nature of the brain metastases resulting in cognitive decline, decline in performance status, and/or inability to complete the imaging study. We have amended the study to enhance accrual by opening to our satellite hospitals as well as those receiving stereotactic radiosurgery for brain metastases.

15. SUBJECT TERMS
18F EF5 PET/CT, breast cancer, brain metastases

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Introduction:

Brain metastases are a frequent neurologic complication of many solid tumors and have been reported to occur in approximately 5-15% of breast cancer patients. As a result of better systemic chemotherapeutic agents which have improved outcomes in breast cancer patients with metastatic disease, metastases in the central nervous system (CNS) have emerged as an important sanctuary site. Treatments to improve outcomes in patients with CNS disease is particularly important now as a growing proportion of patients may experience morbidity and/or mortality from CNS progression at a time when they have controlled extracranial disease. Whole brain radiotherapy is the standard treatment in patients with multiple brain metastases, however, 50% of patients may have local progression of one or more brain metastases at 6 months. Hypoxic and/or anoxic tissue may be a contributing factor to radiation resistance and high rates of local failure after standard radiotherapy. One method of overcoming radiation resistance is through the delivery of escalated doses of radiotherapy through stereotactic radiosurgery (RS), a non-invasive method of delivering highly conformal doses of radiotherapy in a single treatment, which has been demonstrated to improve local control and survival in select patients after WBRT. At present we do not have any method of determining *a priori* which patients may benefit from RS boost. The development of a noninvasive imaging biomarker to identify patients that are at highest risk of local relapse after WBRT would represent a significant step forward in the management of patients with brain metastases from breast cancer. In this study, we propose to use a noninvasive imaging method to detect residual tumor hypoxia in patients receiving WBRT.

Body:

Task 1. To estimate the degree of hypoxia after WBRT in patients with brain metastases from breast cancer as quantified by F18 EF5 PET/CT imaging.

Subtask 1a. Obtain IRB and DOD regulatory approval for prospective clinical trial entitled, "F18 EF5 PET/CT Imaging in patients with brain metastases from breast cancer" treated at the University of Pennsylvania Department of Radiation Oncology (months 1-3).

Protocol full approval was obtained from the University of Pennsylvania IRB on 09/23/11 and from U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 10/12/11. At that time, the temporary transfer of PI responsibility was granted to Dr. Gary Freedman, as the PI (Dr Lin) was going on maternity leave. An amendment was approved by the Penn's IRB on 01/18/12 to return the PI responsibility back to Dr. Lilie Lin on her return from Leave of Absence. U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved this transfer on 02/12/12. Continuing Review of the protocol was approved by Penn's IRB on 11/2/11 and the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 02/12/12.

Subtask 1b. Enroll and recruit patients for the clinical trial (months 3-21).

Accrual goal is 25 subjects; three subjects initially consented to the study. All three were unable to complete the imaging study at the required timepoint. This subject required a prospective protocol exception (deviation): after the subject was consented, it was found that she had very poor venous access and her imaging has been delayed until she can have a port placed. This exception was granted approval by the Penn IRB and by the Data Safety Monitoring Committee on 04/04/12. The Medical Monitor, Dr. Weijing Sun, was notified on 04/04/12 and did not raise objection to the exception. Unfortunately, she subsequently withdrew her consent for the study. The second patient

developed progressive leptomeningeal disease and required spinal radiation leaving her fatigued and unable to complete the study. A third patient did undergo the research brain MRI at the required timepoint, however, when she came in for her F18 EF5 PET/CT imaging, she was unable to lie supine for the duration of the scan due to her progressive pulmonary disease and pleural effusion. There have been no AEs or SAEs. A fourth patient was approached about the study and was interested, however, she developed progressive disease and has been placed on hospice. These occurred during the initial year of the protocol (7/2011-6/2012).

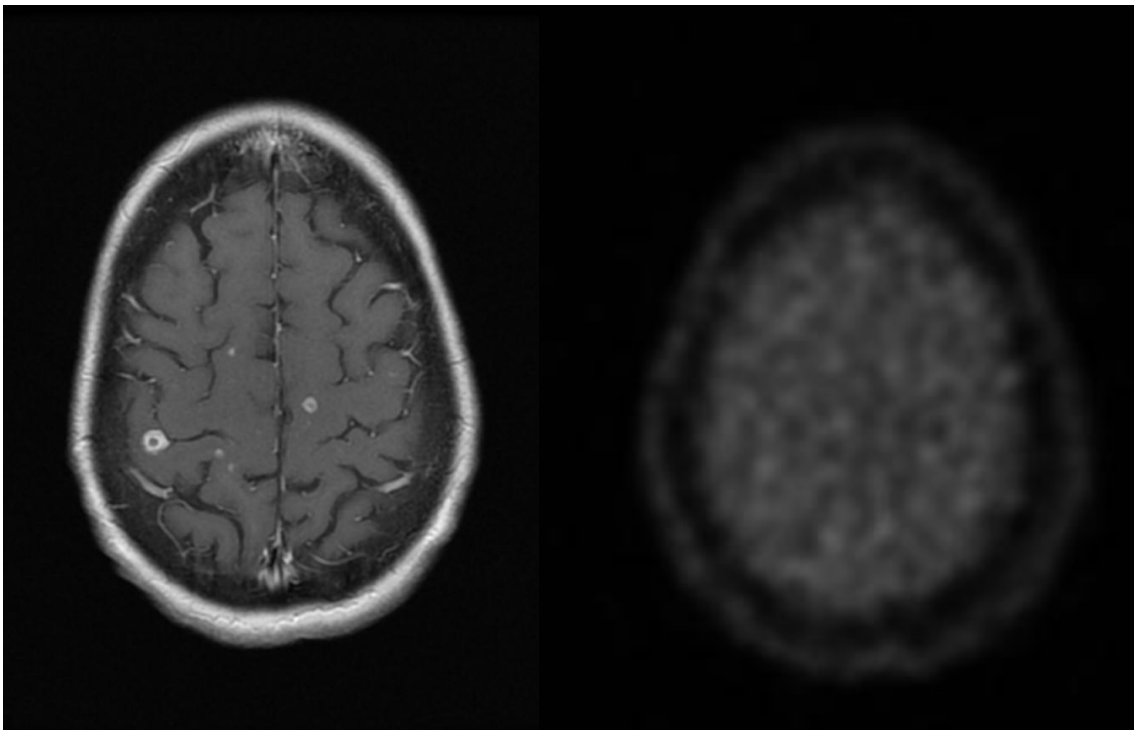
The rate of accrual was challenging with this protocol. At the time this protocol and grant was conceived, whole brain radiotherapy was more often recommended to patients with multiple brain metastases. We have had a change in the paradigm of treatment here at the University of Pennsylvania, where more patients are offered gamma knife radiotherapy upfront rather than whole brain radiotherapy which has impacted our accrual rates. Additionally, though we had several patients that are interested in the study, many of them had concurrent extracranial disease or significant decline in performance status during the time of radiotherapy making them ineligible. Furthermore, we have seen an increase in number of women with metastatic breast cancer present with leptomeningeal disease with or without concurrent intracranial metastases. Patients with leptomeningeal disease oly were not the focus of our proposal and thus these women were not eligible as there would likely be no evidence of abnormal uptake on imaging to be able to follow. Furthermore, patients with better performance status often receive upfront gamma knife radiotherapy instead. These patients were initially ineligible. To address these challenges, we modified the protocol to open the window of imaging to include during radiotherapy as well as up to four weeks post treatment. Additionally, opening up the protocol enrollment to include patients receiving gamma knife radiotherapy was done. Including patients with other types of primary malignancies has also been considered, however, was not approved by the scientific officer.

Two amendments were approved by the University of Pennsylvania IRB with the goal of increasing enrollment. The first amendment received approval on 01/14/2013 and expanded the targeted population to include patients whose treatment plan included stereotactic surgery as well as those receiving whole brain radiation treatment. The second amendment received approval on 06/05/2013 and expanded the targeted population to include patients whose treatment plan includes stereotactic surgery as well as those receiving whole brain radiation treatment who have undergo surgical resection with progression of disease. Adding these subjects did not change the safety profile of the study or the expected risk to subjects.

Thirty-four patients were screened from 7/2012 to 6/2013. Seven patients were found to be eligible. Five of those patients declined as they were not interested in participating in the study. One patient died prior to initiation of therapy. One patient enrolled, however, she subsequently withdrew consent due to progressive disease. Another patient was unable to tolerate the imaging (due to shortness of breath from pulmonary edema) and was withdrawn. During the time period of 7/2013 to 4/2014, 16 patients were screened for the study. Eleven patients were found to be ineligible for a variety of reasons including due to poor performance status, size of disease less than 1 cm. Five patients were eligible and all were approached and one patient underwent imaging (see below for study scan results).

Reportable outcomes
Review of patient enrolled on study:

47 yo woman with multiple (20) brain metastases who received whole brain radiotherapy followed by EF5 PET/CT imaging after whole brain therapy was complete to determine the impact of hypoxia on treatment status (representative slices from pretreatment MRI and 18F ef5 PET/CT scan, figure). No evidence of abnormal uptake was noted in any individual brain metastases. At the 1 month post-treatment mark, MR imaging showed patient's cranial disease to have improved with decreased size in all lesions. At the 6 month post treatment scan, she had continued interval decrease in size as well as number of enhancing intracranial metastases without any new lesions noted. On a 12 month post treatment brain MRi scan, she was noted to have multiple new enhancing lesions in the pons, left frontal periventricular white matter and left cerebellum, measuring 2 to 3 mm in diameter. The previously treated lesions in the supratentorium were decreased in number and enhancement.



Study challenges: The patient cohort that was initially identified was
The study was closed by the Penn CTSRMC (Scientific review committee) on 4/21/2014 due to poor accrual.

Conclusion:
Due to the accrual challenges, changing treatment paradigms for metastatic disease to the CNS, and the patterns of CNS disease (increased leptomeningeal disease, we were unable to complete the study as outlined for the intended population (breast cancer). In the future, it will be difficult to study patients with intracranial disease at a single center even one with reasonable volume.